UNITED STATES PATENT AND TRADEMARK OFFICE

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10/030,722	01/07/2002	Nelson Ruiz-Opazo	50047-006003	3696

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EXAMINER

WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/040,722	Applicant(s) RUIZ-OPAZO, NELSON	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *07 January 2003* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1-5 are pending.

Applicant's traversal, the raw sequence listing, the amendment to claim 1, the addition of claims 2-5, the amendment to the specification in paper no. 7 is acknowledged and considered.

Claim Objections

Claims 2 and 3 are objected to because of the following informalities: A period is missing at the end of each claim.

Claims 1-5 are objected to because of the following informalities: improper grammar for the term "functionally". The term is used as an adjective in the claims, but the term is an adverb.

Appropriate correction is required.

Specification

The amendment filed 1/7/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure is as follows: 1) deletion of references. The deleted references were provided to understand the claimed invention. Applicant has not explained how the deletion fails to introduce new matter.

2) insertion of subject matter from those references. The incorporation of sequences from the cited references is new matter because the incorporation by reference was improper. The

specification does not indicate that the two references the applicant relied on for the nucleotide sequences were in fact relied on for the sequences (incorporation because of the sequences).

3) the sequence listing. For the reasons set forth above the sequence listing is considered new matter.

As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claims 2 and 3 filed on 1/7/03 introduce new subject matter into the application. The application and the originally filed claim as a whole are directed to a method of assaying a test compound using a non-human mammal with a functionally variant hypertension susceptibility gene.

The original specification did not disclose the nucleic acid sequences set forth in SEQ ID NO: 1 and 3. The page cited (pages 4, lines 5-15) for support of the added nucleotide sequences does not support the sequences. The page cited is directed to defining the criteria of EHT susceptibility gene. It is apparent that the applicant at the time the invention was made did not intend or contemplate a method of assaying a test compound using a non-human mammal whose genome comprises SEQ ID NO: 1 and a non-human mammal whose genome comprises SEQ ID NO: 3 as part of the disclosure of their invention. There is no evidence that the applicant was relying on references cited in the specification for their disclosure of any nucleotide sequence in the newly added claims dependent thereof, as it is now claimed, at the time the application was filed.

Applicant's arguments are not applicable to the new ground of 112 first paragraph new matter rejection.

Claim 1 remains and claims 2- 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, as best understood, is readable on a genus of a non-human mammal or a transgenic non-human mammal comprising a functional variant α1 Na,K-ATPase hypertension susceptibility gene, wherein the genus of a non-human mammal is not claimed in a specific manner that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses a functional variant α1 Na,K-ATPase hypertension susceptibility gene, said susceptibility gene meets all the following criteria: 1) identification of a functionally significant structural mutation in the relevant gene: criteria 2), concordance of the observed genetic dysfunction with a pathophysiologic mechanism logical to the hypertension pathogenesis; criteria 3), association of the putative hypertension susceptibility gene with hypertension in validated genetic animal models or human hypertensive patients; and criteria 4), delineation of the mechanistic role in an in vivo model (Herrera, *J. Clin. Invest.*, Vol. 102, 1998, pg. 1102). The specification displays data to support the α1 Na,K-ATPase gene as a susceptibility gene in a salt-sensitive hypertension Dahl S rat, wherein the gene meets the following criteria listed above. However, the genus of a α1 Na,K-ATPase susceptibility

hypertension gene was not described in the original specification in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made. The specification does not disclose how to obtain or make a genus of a non-human mammal or a transgenic non-human mammal comprising a functional variant α1 Na,K-ATPase hypertension susceptibility gene. The art of record is absent for how to obtain or make a genus of the claimed non-human mammals.

It is apparent that on the basis of the applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a non-human mammal or transgenic non-human mammal comprising a functional variant hypertension susceptibility gene and/or a functionally variant hypertension susceptibility gene expressed as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of a non-human mammal and/or a transgenic non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of hypertension susceptibility genes that must exhibit the disclosed biological functions as contemplated by the claims.

The as-filed specification does not provide sufficient support for the present claimed invention directed to a genus of a non-human mammal comprising a functional variant hypertension susceptibility gene, except for the salt-sensitive hypertension Dahl S rat. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of a non-human mammal or a

transgenic non-human mammal comprising a functional variant α1 Na,K-ATPase hypertension susceptibility gene that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a predictable representative number of species of the claimed non-human mammal or a transgenic non-human mammal that must exhibit the contemplated biological function of the claimed genus of non-human mammals, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 1/7/03 have been fully considered but they are not persuasive. The specification does not disclose how to obtain or make a representative number of species of the claimed genus of non-human mammals. The as-filed specification does not provide an adequate written description of a representative number of species of non-human mammals whose genome comprises a functionally variant α1 Na,K-ATPase hypertension

susceptibility gene. A representative number of species is required for an adequate description as embraced by the claimed genus of non-human mammals and is not described sufficiently in the specification nor conventional in the prior art. A mere statement asserting that the Dahl S rat comprising a functionally variant α1 Na,K-ATPase hypertension susceptibility gene is a representative member of the genus of non-human mammals without providing that the hypertension susceptibility gene from Dahl S rat is the same gene found in other mammals does not lend evidentiary support for a skilled artisan to have recognized that applicant was in possession of the claimed genus, particularly since a representative number of species is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine other non-human mammals of the representative number of species of α1 Na,K-ATPase hypertension susceptibility gene on the basis of the only disclosure of one α1 Na,K-ATPase hypertension susceptibility gene from Dahl S rat.

Vas-Cath Inc. v Mhurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purpose of the 'written description' inquiry, *whatever is now claimed.*" The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, See MPEP 2163).

With the exception of the α1 Na,K-ATPase hypertension susceptibility gene from Dahl S rat, the skilled artisan cannot envision the detailed genus of non-human mammal whose genome comprises a functionally variant α1 Na,K-ATPase hypertension susceptibility gene, regardless of the complexity or the simplicity of the method of production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential

method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v Chugai Pharmaceutical Co. Ltd., 18 USPQ 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification only provided the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997): *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement 'by describing the invention, with al it claimed limitations, not that which make it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Lockwood*, 107F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmid and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Dir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. At 1170, 25 USPQ at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information, concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is not further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes; as the example does, does not necessarily describe the cDNA itself. No sequence information indication which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA

in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only the Dahl S rat whose genome comprises an α1 Na,K-ATPase hypertension susceptibility gene, but not the full breadth of the claim (or none of the non-human mammals encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The specie specifically disclosed is not representative of the genus because the genus is highly variant. Therefore, the rejection under 112 written description remains.

Claim 1 remains and claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabled for: A method of assaying a test compound for its effect on hypertension parameters, said method comprising:

a) providing a Dahl Salt-sensitive^{HSD} rat;

b) administering a test compound to the rat in step a); and

c) determining whether the test compound modulates hypertension parameters in the rat relative to the hypertension parameters in a rat containing a wild-type α1 Na,K-ATPase gene and is not enabled for a method of assaying a test compound for an effect on hypertension parameters using any non-human mammal whose genome comprises a functionally variant α1 Na,K-ATPase hypertension susceptibility gene. The as-filed specification does not reasonably provide enablement for the presently pending claims encompassing any other functionally variant hypertension susceptibility gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with this claim.

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of a non-human mammal whose genome comprises a functional variant α1 Na,K-ATPase hypertension susceptibility gene) as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, *e.g.* a method of assaying a test compound, using a non-human mammal whose genome comprises a functionally variant α1 Na,K-ATPase hypertension susceptibility gene.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention relates to a method of a method of assaying a test compound, said method comprising: a) providing a non-human mammal whose genome comprises an α1 Na,K-ATPase hypertension susceptibility gene, b) administering said test compound to said non-human mammal, and c) determining whether said test compound affects hypertension parameters in said non-human animal relative to a non-human mammal containing a wild-type α1 Na,K-ATPase gene. The claimed invention lies in the field of using a non-human mammal comprising a hypertension susceptibility gene. In addition, in view of the as-filed specification, the claimed invention also lies in the field of using a transgenic non-human mammal comprising a heterologous α1 Na,K-ATPase hypertension susceptibility gene.

There are concerns set forth by the art of record for predicting a protein's tertiary structure based on its polypeptide sequence, identifying hypertension genes, and the production of transgenic non-human mammals.

The state of the art for hypertension, as exemplified by Herrera et al., J. Clin. Invest. Vol. 102, 1998, pp. 1102-1111, display that:

> Essential hypertension (EHT) is a paradigmatic, complex, and multifactorial condition. Genes that mediate EHT will therefore be difficult to isolate and characterize, requiring multiple lines of evidence to prove their roles in EHT pathogenesis. Cognizant of these issues, delineation of a putative EHT susceptibility gene should meet the following criteria set forth on page 1102, right column, 1st paragraph. See page 1102.

In addition, the state of the art for predicting tertiary structure (biological activity) from a polypeptide sequence, as exemplified by Chiu et al., *Folding and Design*, Vol. 3, pg. 223-228, May 1998, displays major consideration for predicting a protein tertiary structure involve issues that include:

> Predicting the three-dimensional conformation of a correctly folded protein can be divided into two distinct steps: the construction of a fitness function to evaluate the various conformations: and the search through various possible conformations for the "best" prediction most likely to represent the native state. Neither part of this problem has proven particularly tractable. The development of a general method for the prediction of protein tertiary structure based on the protein sequence remains, unfortunately, one of the great-unsolved problems of computational biophysics (pg. 223).

Furthermore, with respect to the state of the art for transgenic non-human animals, the starting material for the method is a non-human mammal and the transgenic mammal would require the production of transgenic non-human mammals encompassing the use of embryonic stem (ES) cell technology or using pro-nuclear injection. The state of the art at the time

application was filed for predicting a phenotype in transgenic non-human mammals using pro-nuclear injection or ES technology was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. See page 119.

Therefore, the art of record for the production of transgenic non-human mammal or non-human mammal whose genome comprises α1 Na,K-ATPase hypertension susceptible gene is considered unpredictable at the time the application was filed.

The as-filed specification contemplates that the invention features a genus of a non-human mammal comprising a α1 Na,K-ATPase hypertension susceptibility gene. The specification provides working examples encompassing producing a transgenic rat using microinjection of a nucleic acid encoding an unspecified alpha1 NA, K-ATPase protein and methods of studying a high salt diet using the transgenic rats and Dahl S hypertensive rat (pages 8-24). The specification does not disclose what alpha1 NA, K-ATPase cDNA was used or how to obtain the cDNA used in the working example.

Furthermore, with respect to the claimed invention encompassing a hypertension susceptibility gene, the as-filed specification provides sufficient guidance for one skilled in the art to use a Dahl Salt Sensitive^{HSD} rat in the claimed methods. However, the specification does not provide sufficient guidance for making or using a genus of non-human mammals whose

genome comprises a α1 Na,K-ATPase hypertension susceptibility gene in the claimed methods. The prior art teaches that essential hypertension (EHT) is a paradigmatic complex and multifactorial condition (Herrera et al., *J. Clin. Invest*, Vol. 102, 1998, pg. 1102-1111). Genes that mediate EHT will therefore be difficult to isolate and characterize, requiring multiple lines of evidence to prove their roles in EHT pathogenesis (page 1102). With respect to the art of record, it is not apparent how the as-filed specification is enabled for making and using any other non-human mammal whose genome comprises a hypertension susceptibility gene, except the Dahl Salt Sensitive rat.

The essential material of the claimed invention is the requirement of staring material (e.g. a non-human mammal or a transgenic non-human mammal comprising a hypertension susceptibility gene). It is not apparent to one skilled in the art how to make any non-human mammal with a hypertension susceptibility gene due to the art of record concerning the unpredictability of determining a phenotype in transgenic non-human mammals and obtaining a genus of hypertension susceptibility gene. More specifically as to the lack of reasonable extrapolation from the biological functional of the hypertension susceptibility gene from Dahl S rat to a genus of non-human mammals whose genome comprises α1 Na,K-ATPase gene, it would take one skilled in art an undue amount of experimentation to make and/or use the claimed invention. Especially with lack of sufficient guidance required for predicting any protein tertiary structure based on a protein structure. At the time the application was filed, predicting any protein tertiary structure based on a protein structure was considered to be unpredictable due to significant problems in several areas (see Chui et al.).

Thus, given the lack of sufficient guidance cited in the claims and the art of record, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the full breath of the claimed invention on the basis of applicant's disclosure. Even if it has been shown that the Dahl Salt Sensitive^{HSD} rat has a susceptibility hypertension gene (α1 Na,K-ATPase). It is not apparent as to how the Dahl S rat is reasonably extrapolated to the full scope of the claimed invention encompassing any other hypertension susceptibility gene, except the α1 Na,K-ATPase gene in Dahl Salt Sensitive^{HSD} rat, which is not a general phenomenon, and given the doubts expressed in the art of record.

Furthermore, with respect to claims 1-5, as the claimed invention encompass a transgenic non-human mammal comprising a hypertension susceptibility gene using any technology, and the as-filed specification fails to teach the production of a representative number of transgenic non-human mammals for use in the claimed method, the art of record supports that the Na,K-ATPase gene from Dahl S rat would display EHT phenotype. In view of the concerns set forth by the art of record, the examples in the specification do not reasonably address the concerns put forth by art of record encompassing a method for producing any transgenic non-human mammal whose genome comprises a susceptibility hypertension gene (α1 Na,K-ATPase) for use in the claimed method of assaying a test compound. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any transgenic non-human mammal comprising a hypertension susceptibility gene (α1 Na,K-ATPase) in its genome. In addition, in view of the concerns stated above encompassing microinjection and random integration into a non-human mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably

extrapolate from random integration to determining if a transgene is inserted at the correct site and is expressed at a level sufficient enough to produce a non-human mammal displaying EHT phenotype for use in a method of assaying a test compound that modulates hypertension in a mammal.

As the as-filed specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human mammals as claimed, one skilled in the art would not be able to rely on prior art for an attempt to produce the genus of transgenic non-human mammals. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic non-human mammal comprising a transgene of interest (e.g. hypertension susceptibility gene); it is not predictable if the transgene would be expressed at a level and specificity sufficient to be used in a method of assaying a test compound that modulates hypertension. For example, the level and specificity of expression of a transgene (e.g. hypertension susceptibility gene) as well as the resulting phenotype of the transgenic non-human mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified non-human animals, which exhibit a particular phenotype (EHT). This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the

field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human mammals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Therefore, the art of record teaches that the production of transgenic non-human mammal with a desired phenotype (EHT) is considered unpredictable.

In addition, given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic non-human mammal that expresses a hypertension susceptibility gene other than a Dahl S rat, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic non-human mammal comprising a transgenic sequence encoding a hypertension susceptibility gene and which expresses the protein in the

transgenic non-human mammal at the levels of the claimed product, the consequences of that production, and therefore, the resulting use in any method of assaying a test compound that could modulate hypertension.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic non-human mammals comprising a hypertension susceptibility gene. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any contemplated transgenic non-human mammal of the invention other than a Dahl S rat. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic non-human mammal comprising a hypertension susceptibility gene.

[Note that although the claimed transgenic non-human mammal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic non-human animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic non-mammal would serve if the transgene (e.g. hypertension susceptibility gene) is not expressed at a sufficient level for a resulting phenotype).]

Thus, in view of the In re Wands' Factors, the disclosure is enabled for using a Dahl S rat in method of assaying a test compound for an effect on hypertension parameters and is not enabled for the full scope of the claimed invention because in view of the undue quantity of experimentation necessary to determine the parameters listed above for the starting material (non-human mammal or transgenic non-human mammal), the lack of direction or sufficient guidance provided by the as-filed specification for the production of any transgenic non-human mammal or non-human mammal with a particular phenotype other than a Dahl S rat. Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of a genus of transgenic non-human mammal, in particular when the expression of the must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human mammals of any species other than rat, and the breadth of the claims drawn to any transgenic non-human mammal or non-human mammal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the full scope of the claimed invention.

Applicant's arguments filed 1/7/03 have been fully considered but they are not persuasive. The specification does not teach one skilled in the art how to make or obtain a genus of non-human mammals whose genome comprises an α1 Na,K-ATPase hypertension susceptibility gene for use in a method of assaying test compounds for an effect on hypertension parameters. The specification teaches how to make a transgenic rat whose genome comprises an unspecified α1 Na,K-ATPase hypertension susceptibility gene or a Dahl S rat. The as-filed specification does not disclose how to obtain or make the starting material (a functionally variant α1 Na,K-ATPase hypertension susceptibility gene) from a representative number of species or

obtain a representative number of species of non-human mammals with a functionally variant α1 Na,K-ATPase hypertension susceptibility gene. The art of record at the time the application was filed was absent for how to obtain non-human mammals with the claimed gene.

Furthermore, with respect to the claims reading on making and using a transgenic non-human mammal, the specification teaches how to make a transgenic rat whose genome comprises an unspecified α1 Na,K-ATPase hypertension susceptibility gene. The specification does not disclose what gene was used in the working examples or how to obtain the gene. The specification does not provide sufficient guidance or factual evidence for one skilled in the art to reasonably extrapolate from the transgenic rat to a genus of the claimed transgenic non-human mammals. The art of record teaches the unpredictability of determining a phenotype be inserting a transgene into a non-human mammal. Sigmund (Arterioscler. Thomb. Vac., Biol, Vol. 20:1425-1429, 2000) and Cutler Linder (Lab Animal, Vol. 30: 34-39, 2001) further support the unpredictability of determining a phenotype when inserting a transgene into a non-human mammal.

The as-filed specification does not provide sufficient guidance and/or factual evidence for how to overcome the unpredictability of making or obtaining a genus of claimed non-human mammals stated by the art of record.

In addition, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment…; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171,

25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

On this record, it is apparent that the specification and the applicants' traversal (See page 21 of traversal, which states, "a determination that the transgene is adequately expressed and biologically active would require only routine experimentation") provide no more than a plan or invitation in view of the art of record exemplifying the unpredictability of making a genus of non-human mammals whose genome comprises a functionally variant α1 Na,K-ATPase hypertension susceptibility gene in the claimed methods, for those skilled in the art to experiment with transgenic protocols so as to provide the claimed a representative number of species of non-human mammals for use as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what gene is required for different non-human mammals, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the scope listed above to the full breadth of claimed invention.

Thus, in view of the In Re Wands Factors, the claimed invention is only enabled for the scope listed above under the scope in the 112 enablement rejection and not for the full scope of the claimed invention.

Applicant's argument, see page 23, filed on 1/7/03, with respect to the rejection for claim 1 under 112 second paragraph has been fully considered and are persuasive. The rejection of claim 1 has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 remains and claims 2, 3, 4, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Medvedev et al. (*J. Auton. Nerv Syst*, Vol. 72, 1998, pp. 170-6); Vesely (US Patent 5,691,310); or Somova et al. (*Methods Find Exp Clin Pharamcol*, Vol 21, 1999, pp. 412-5) taken with Herrera et al., (*J. Clin. Invest.* Vol. 102, 1998, pp. 1102-1111). Somova teaches a method to evaluate glucose metabolism and insulin sensitivity in the Dahl genetic salt-

sensitive rat model of hypertension (abstract). Vesely teaches that in vivo animal testing demonstrate that potent natriuretic, diuretic, and blood pressure reducing effects exhibited by two peptide hormones originating for the human atrial factor (ANF) prohormone consisting of amino acid 1-30 and 31-67 of the human prohormone while another peptide hormone consisting of amino acids 79-98 of the human ANF prohormone has diuretic, kaliuretic and blood pressure lowering properties (columns 3, lines 61-66 and column 4, lines 1-5). In addition, Medvedev investigated the chronopharmacological dependence of dose-dependent hypotensive and cardiochronotropic effects of the imidazoline-like drugs in stroke-prone spontaneously hypertensive rats (abstract). However, Somova, Vesely, or Medvedev do not describe a method of assaying a chemical compound using a Dahl Salt-sensitive^{HSD} rat or transgenic rat whose genome comprises susceptibility hypertension gene (α1 Na,K-ATPase gene).

However, at the time the invention was made, Herrera displayed a Dahl Salt-sensitive^{HSD} rat and a transgenic rat with the susceptibility hypertension gene (α1 Na,K-ATPase gene) in its genome.

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill, as a matter of obvious design choice to combine the teaching of either Somova, Vesely, or Medvedev taken with Herrera to test chemical compounds in Dahl Salt-senstive^{HSD} rats or transgenic rat with the α1 Na,K-ATPase gene. One of ordinary skill in the art would have been motivated to study how chemical compounds modulate hypertension parameters in the Dahl Salt-sensitive^{HSD} rat or transgenic rat with the α1 Na,K-ATPase gene particularly since assaying chemical compounds in hypertensive rats was well known in the art as taught by either Somova or Medvedev.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

The Declaration of Dr. Ruiz-Opazo under 37 CFR 1.132 filed 1/7/03 is insufficient to overcome the rejection of claim 1 based upon 103(a) rejection as set forth in the last Office action because: the declaration was not signed by Dr. Ruiz-Opazo.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE PH.D
PRIMARY EXAMINER